Genetic Polymorphism of CYP2A6 and its Effects on the Tobacco-related Lung Cancer Risk

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During the course of pharmacokinetic studies of SM12502 which was under development as an anti-PAF agent, we found that there were three subjects who showed a slow metabolic phenotype in its pharmacokinetics. Since this compound was oxidized specifically by CYP2A6, we analyzed the genes for CYP2A6 of the three subjects. The results indicated that the three subjects possessed the whole *CYP2A6* gene deletion genotype. Accordingly, we developed a gene diagnosis method for this genotype.

Genetically engineered *Salmonella* YG7108 cells expressing human CYP2A6 or CYP2E1 together with the NADPH-CYP reductase were established to compare the mutagen-producing capacity of these enzymes for various *N*-nitrosamines. We found that CYP2E1 was responsible for the metabolic activation of *N*-nitrosamines with relatively short alkyl chains, whereas CYP2A6 was involved in the metabolic activation of *N*-nitrosamines possessing relatively bulky alkyl chains such as a tobacco-specific nitrosamine, NNK, which has been known to cause lung tumor in rodents.

As mentioned above, we found an entire *CYP2A6* gene deletion (D)-type genetic polymorphism in a Japanese population by analyzing the gene of poor metabolizers (PM)

against a drug SM-12502. Thus, to examine a working hypothesis that individuals possessing the D-type have the reduced risk of lung cancer due to the lack of the metabolic activation of certain carcinogens in tobacco smoke, a case-control study was performed. The results indicated the existence of a significant (p=0.004) association between the CYP2A6 genotype and a lung cancer risk in smokers. In contrast, there was no significant (p=0.45) relationship between them in non-smokers. Odds ratio was 0.17 in a group with homozygous D-type (D/D), suggesting that smokers with the D/D genotype have lower risk of lung cancer. Cigarette smoking has been known to cause squamous cell and small cell carcinomas. To clarify the type of lung cancer in relation to CYP2A6 genotypes, the cancer patients were classified into two groups according to pathological classification of cancer, namely, patients with small cell carcinoma and non-small cell carcinoma. The latter patient group was further divided into two groups containing squamous cell carcinoma or non-squamous cell carcinoma. A significant (p=0.029) difference in the distribution of the CYP2A6 genotypes was seen between controls and patients with the squamous cell carcinoma. Moreover, there was no patient with the D/D type in groups suffered from squamous cell carcinoma and small cell carcinoma, indicating that smokers with the D/D genotype have the reduced risk of these tobacco-related lung cancers.